N-Nitrosodiphenylamine; CASRN 86-30-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR N-Nitrosodiphenylamine

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/31/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — N-Nitrosodiphenylamine
CASRN — 86-30-6

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — N-Nitrosodiphenylamine
CASRN — 86-30-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — N-Nitrosodiphenylamine
CASRN — 86-30-6
Last Revised — 03/31/1987

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Increased incidence of bladder tumors in male and female rats and reticulum cell sarcomas in mice, and structural relationship to carcinogenic nitrosamines

II.A.2. Human Carcinogenicity Data

Inadequate. Human exposure to nitrosamines results from contact with mixtures containing these compounds (e.g., cutting oils, tobacco products). Because of potential confounding by the other substances in these mixtures, data are of limited use in the evaluation of carcinogenicity of individual nitrosamines.

II.A.3. Animal Carcinogenicity Data

N-nitrosodiphenylamine (98% pure containing two unspecified impurities) was administered at 0, 1000 or 4000 ppm in diet to groups of 50 F344 rats/ sex. Matched controls consisted of 20 rats/sex. Dose-related mortality was noted in females. Statistically increased incidence of urinary bladder transitional cell carcinomas was observed in both sexes. Epithelial hyperplasia and squamous metaplasia also occurred, as did integumentary fibromas in males (NCI, 1979).

In the same study no increased tumor incidence was observed in B6C3F1 mice receiving dietary doses of 10,000 and 20,000 ppm (males) or 2475 and 6139 ppm (TWA, females). Likewise, no evidence of carcinogenicity was observed in BD rats administered 120 mg nitrosodiphenylamine/kg in water for 541 days or in male Wistar rats gavaged with 1.07 mg/day in 1.1% aqueous methylcellulose 5 days/week for 45 weeks (Druckrey et al., 1967; Argus and Hoch-Ligeti, 1961). Neither B6C3F1 nor B6AKF1 mice showed statistically significant increases in tumor incidence following gavage with 1000 mg/kg/day from day 7-28 of age followed by dietary exposure to 3769 ppm until weeks 77-79 of life (BRL, 1968; Innes et al., 1969). Weekly topical application of diphenylnitrosoamine for 20 weeks did not induce tumors in hr/hr Oslo mice, nor did weekly i.p. injection of 2.5 mg in PEG 400 (Iverson, 1980; Boyland et al., 1968). A single s.c. injection of 1000 mg/kg/day resulted in significantly increased incidence of reticulum cell sarcomas in male B6C3F1 mice, but not in females or B6AKF1 mice of either gender (BRL, 1968).

II.A.4. Supporting Data for Carcinogenicity

Nitrosodiphenylamine has produced mixed responses in genetic toxicology tests. It was negative in bacterial mutation assays, mutation assays in V79 and CHO and mouse lymphoma cells and SCE in CHO cells (IARC, 1982). Positive responses have been obtained for several endpoints in S. cerevisiae (de Serres and Hoffmann, 1981) and in DNA damage assays in rat hepatocytes (Althaus et al., 1982; Sina et al., 1983). N-nitrosodiphenylamine produced transformation of Syrian hamster embryo cells, BHK cells and F344 rat embryo cells infected with Rauscher murine leukemia viruses (Pienta and Kawalek, 1981; Daniel and Dehnel, 1981; Dunkel et al., 1981).

N-nitrosodiphenylamine is structurally related to carcinogenic nitrosamines.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 4.9E-3/mg/kg/day

Drinking Water Unit Risk — 1.4E-7/ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	7E+2 ug/L
E-5 (1 in 100,000)	7E+1 ug/L
E-6 (1 in 1,000,000)	7E+0 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: transitional cell carcinoma of the bladder
Test animals: Rat/F344, female
Route: drinking water
Reference: NCI, 1979

Administered Dose		Human Equivalent Dose (mg/kg)/day	Tumor Incidence
ppm	**(mg/kg)/day**		

0	0	0	0/18
1000	50	7.7	0/48
4000	200	30.6	40/49

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The unit risk should not be used if the water concentration exceeds 7E+4 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of animals were treated and observed for their lifetime. Significant increases in tumor incidence were observed only in high-dose animals. NCI noted that the mechanism by which bladder tumors were induced (e.g., calculus formation or nitrosation of amines in feed) is not known.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The 1986 Health and Environmental Effects Profile for Nitrosoamines has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 02/11/1987

Verification Date — 02/11/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for N-Nitrosodiphenylamine conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — N-Nitrosodiphenylamine
CASRN — 86-30-6

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

Althaus, F.R., S.D. Lawrence, G.L. Sattler, D.G. Longfellow and H.C. Pitot. 1982. Chemical quantification of unscheduled DNA synthesis in cultured hepatocytes as an assay for the rapid screening of potential chemical carcinogens. Cancer Res. 42(8): 3010-3015.

Argus, M.F. and C. Hoch-Ligeti. 1961. Comparative study of the carcinogenic activity of nitrosamines. J. Natl. Cancer Inst. 27: 695-709.

Boyland, D., R.L. Carter, J.W. Gorrod and F.J.C. Roe. 1968. Carcinogenic properties of certain rubber additives. Eur. J. Cancer. 4(2): 233-239.

BRL (Bionetics Research Laboratory). 1968. Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Vol. 1, Carcinogenic study. NTIS PB 223-159.

Daniel, M.R. and J.M. Dehnel. 1981. Cell transformation test with baby hamster kidney cells. Prog. Mutat. Res. 1: 626-637.

de Serres, F.J. and G.R. Hoffmann. 1981. Summary report on the performance of yeast assays. Prog. Mutat. Res. 1: 68-76.

Druckrey, H., R. Preussmann, S. Ivankovic and D. Schmael. 1967. Organotropism and carcinogenic activities of 65 different N-Nitrosodi compounds on BD-rats. Z. Kerbsforsch. 69(2): 103-201.

Dunkel, V.C., R.J. Pienta, A. Sivak and K.A. Traul. 1981. Comparative neoplastic transformation responses of Balb/3T3 cells, Syrian hamster embryo cells, and Rauscher murine leukemia virus-infected Fischer 344 rat embryo cells to chemical carcinogens. J. Natl. Cancer Inst. 67(6): 1303-1315.

IARC (International Agency for Research on Cancer). 1982. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man N-Nitrosodiphenylamine. Some Aromatic Amines, Anthroquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking Water and Dental Preparations. WHO, IARC, Vol. 27, Lyon, France. p. 213-225.

Innes, J.R.M., B.M. Ulland, M.G. Valeria, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice : A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Iverson, O.H. 1980. Tumorigenicity of N-nitroso-diaethyl, -dimethyl and -diphenyl-amines in skin painting experiments. A study utilizing the tetrazolium test and skin applications on hairless mice. Eur. J. Cancer. 16(5): 695-698.

NCI (National Cancer Institute). 1979. Bioassay of N-Nitrosodiphenylamine for Possible Carcinogenicity. NCI Carcinogenesis Technical Report Series No. 164. NIH 79-1720. NTIS PB 298-275.

Pienta, R.J. and J.C. Kawalek. 1981. Transformation of hamster embryo cells by aromatic amines. Natl. Cancer Inst. Monogr. 58: 243-251.

Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113(5): 357-391.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Nitrosamines. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. NTIS PB 81-117756.

U.S. EPA. 1986. Health and Environmental Effects Profile for Nitrosamines. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

VII. Revision History

Substance Name — N-Nitrosodiphenylamine
CASRN — 86-30-6

Date	Section	Description
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — N-Nitrosodiphenylamine
CASRN — 86-30-6
Last Revised — 03/31/1987

- 86-30-6
- BENZENAMINE, N-NITROSO-N-PHENYL-
- CURETARD A
- DELAC J
- DIPHENYLAMINE, N-NITROSO-
- DIPHENYLNITROSAMIN
- DIPHENYLNITROSAMINE
- DIPHENYL N-NITROSOAMINE
- NAUGARD TJB
- NCI-C02880
- NDPA
- NDPhA
- NITROSODIPHENYLAMINE
- Nitrosodiphenylamine, N-
- NITROUS DIPHENYLAMIDE
- N,N-DIPHENYLNITROSAMINE
- N-NITROSODIFENYLAMIN
- N-Nitrosodiphenylamine
- N-NITROSO-N-PHENYLANILINE

- REDAX
- RETARDER J
- TJB
- VULCALENT A
- VULCATARD
- VULCATARD A
- VULKALENT A
- VULTROL